REMARKS

Claims 1, 4 to 6, 9 to 13, 17, 21, 24, 25, 36, 37, and 101 are pending in this patent application. No claims have been amended, added, or canceled, herein. Applicants respectfully request reconsideration of the rejections of record in view of the following remarks.

Alleged Obviousness

Claims 1, 4 to 6, 9 to 13, 17, 21, 24, 25, 36, 37, and 101 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by published U.S. patent application number US 2004/0259247 ("the Tuschl application") in view of published U.S. patent application number US 2002/0162126 ("the Beach Application") and Manoharan *et al.*, *Tetrahedron Letter*, 1995, 36, 3651-3654 ("the Manoharan article"). Applicants respectfully request reconsideration and withdrawal of this rejection because the claimed compositions would not have been obvious to those of ordinary skill in the art at the time of the invention in light of the teachings provided in the cited references.

The claims recite, *inter alia*, compositions that comprise a complementary pair of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other. At least one of the first and second oligomeric compounds comprises at least one steroid conjugate moiety attached to a terminal monomeric subunit of the oligomeric compound. The cited references, when considered individually or in combination, fail to render such compositions *prima facie* obvious.

Because obviousness is necessarily determined as of the time of invention, it is fundamental that the Office avoid using hindsight when assessing obviousness.[1] In this regard, the Supreme Court recently indicated in *KSR Int'l Co. v. Teleflex* that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already

[1] See e.g., *KSR Int'l Co. v. Teleflex*, 127 S.Ct. 1727, (2007) (warning against "the distortion caused by hindsight bias . . . and arguments reliant on *ex post* reasoning."); 35 U.S.C. § 103 (requiring determination of whether an invention "would have been obvious at the time the invention was made.").

known."[2] To avoid the trap of hindsight, a finding of obviousness therefore requires the Office to identify "a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the [known] elements *in the way the claimed new invention does*."[3] In applying these principles to a case involving chemical compounds, the Federal Circuit held in *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd* that "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[4] Moreover, according to the Federal Circuit "an invention would not be deemed obvious if all that was suggested 'was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.'"[5]

In the present case, the Office has failed to provide reasons why those of ordinary skill would have combined particular aspects of the cited references to arrive at the claimed compositions. Instead, the Office relies on hindsight to pick and choose elements from the vast, unpredictable, and in some instances contrary, art, to arrive at the claimed subject matter, and the Office has therefore failed to properly establish *prima facie* obviousness. The cited references, in fact, fail to render the claimed compositions obvious, for at least the following reasons.

The Tuschl application describes double-stranded RNA molecules that mediate target-specific RNA interference or other target-specific nucleic acid modifications, such as DNA methylation.[6] The Tuschl application indicates that the RNA molecules may contain at least one modified nucleotide analogue, and such nucleotide analogue(s) "may be located at positions where the target-specific activity, e.g., the RNAi mediating activity is not substantially effected [*sic*], e.g. in a region at the 5'-end and/or the 3'-end of the double stranded RNA molecule."[7] Significantly, however, the Tuschl application indicates that in

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[2] *Id.*
[3] *Id.* (emphasis added).
[4] *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added).
[5] *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 83 USPQ 2d 1289, 1305 (Fed. Cir. 2007), (citing *In re O'Farrell*, 853F.2d 894, 903 (Fed. Cir. 1988)).
[6] Paragraph 8.
[7] Paragraph 15.

preferred double-stranded RNA molecules "[t]he 5'-terminus preferably comprises a phosphate, diphosphate, triphosphate or hydroxyl group."[8] The nucleotide analogue(s) described in the Tuschl application may comprise vast genuses of possible nucleoside modifications. For example, the Tuschl application indicates that possible modifications include sugar, backbone, and nucleobase modifications, and provides numerous examples of each of such modifications.[9] The Tuschl application fails to describe or suggest, however, modifying siRNA molecules by attachment of one or more conjugate moieties, much less attachment of conjugate moieties to a terminal monomeric subunit of at least one of the oligomeric compounds of siRNA molecules. The Tuschl application accordingly contains no teaching or suggestion whatsoever of conjugation of steroid moieties to the ends of double-stranded siRNA molecules.

The Office attempts to fill the substantial gaps left by the Tuschl application by relying on two secondary references, the Beach application and the Manoharan article. These references fail to compensate for the deficiencies of the Tuschl application, however. Notably, with respect to the Beach application, as with the Tuschl application (discussed above), the Beach application fails to describe or suggest conjugation of steroid moieties to the ends of double-stranded siRNA molecules. Instead, the Beach application describes methods for attenuating expression of a target gene in a cell by introducing double stranded RNA into the cell.[10] The Beach application teaches that the double-stranded RNA construct can be introduced into cells using "methods known in the art," which are said to include injection into cells of a solution containing the double stranded RNA construct, bombardment of cells by particles covered by the double stranded RNA construct, soaking the cells or an organism in a solution of the RNA construct, electroporation of cell membranes in the presence of the double stranded RNA construct, and infection of cells by viral particles into which viral constructs containing expression constructs that encode the double stranded RNA construct are packaged, followed by transcription of double stranded RNA construct encoded by the expression construct.[11] The Beach application indicates that other methods known in the art for introducing nucleic acids to cells may be used for the double stranded RNAs,

[8] Paragraph 12.
[9] Paragraphs 15 to 16.
[10] Paragraphs 7 to 10.
[11] Paragraph 139.

"such as lipid-mediated carrier transport, chemicalmediated transport, such as calcium phosphate, and the like."[12] The application concludes this discussion by stating that "the dsRNA construct may be introduced along with components that perform one or more of the following activities: enhance RNA uptake by the cell, promote annealing of the duplex strands, stabilize the annealed strands, or other-wise increase inhibition of the target gene."[13] The Beach application thus provides a listing of methods known in the art for introduction of nucleic acids into cells, which include "lipid-mediated carrier transport."[14] Significantly, the Beach application does not teach or suggest *conjugation* of a lipid moiety to a double-stranded siRNA molecule, but indicates only that lipid-mediated transport mechanisms are one possible way that double-stranded RNAs can be introduced into cells. Moreover, the Beach application provides no teaching or suggestion that conjugation of lipid moieties to duplex RNA molecules would be a viable means for enhancing uptake of the molecules into cells. Upon review of the Tuschl and Beach applications, those skilled in the art therefore would have had no reason to conjugate one or more lipid moieties to siRNA oligomeric compounds, because the combined teachings of the Tuschl and Beach applications provide no suggestion that such chemical modification of siRNA molecules would impart any desirable properties while preserving the biological activity of the molecules.

The Manoharan article does not compensate for the deficiencies of the Tuschl and Beach applications. Notably, the Manoharan article fails to describe or suggest complementary pairs of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other, much less describe conjugation of steroids to a terminal monomeric subunit of such double-stranded siRNA oligomeric compounds. Significantly, the Manoharan article describes incorporation of lipid-conjugated nucleosides into *single-stranded* antisense *DNA* oligonucleotides, which exert their biological activity by serving as substrates for RNase H.

As understood by those skilled in the art, RNase H is an enzyme that cleaves the RNA strand of a DNA/RNA duplex. Accordingly, antisense oligonucleotides that reduce a target RNA in a cell by relying on RNase H activity must mimic a DNA strand. Such compounds

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[12] *Id.*
[13] *Id.*
[14] Paragraph 139.

were known at the time of present invention to have certain structural requirements. For example, RNase H dependent antisense oligonucleotides must have a stretch of DNA (2'-deoxy) or DNA-like nucleosides. In contrast, the Tuschl and Beach applications describe *double stranded RNA* molecules (rather than single stranded DNA molecules) whose biological activity operates through the RNA interference (RNAi) pathway. Not surprisingly, the structural requirements of substrates utilized in this mechanism differ from those of RNase H. In this regard, the siRNA molecules described in the Tuschl and Beach applications are double-stranded compounds that comprise at least some RNA nucleosides. These compounds do not have a region of DNA or DNA-like nucleosides because such region is unnecessary and would not activate RNAi. Likewise, the Manoharan article, which describes RNase H-dependent oligonucleotides, does not describe double-stranded RNA-containing compounds such as those described in the Tuschl and Beach applications. The two mechanisms of target mRNA reduction are sufficiently different that there would have been no reason to believe that useful chemical modifications present in the substrates for one mechanism would be useful for the substrates utilized in the other. If one were, nevertheless, to have looked to the chemical modifications useful for RNase H substrates, and were to have tried them in RNAi substrates, one would have chosen compounds that failed to activate RNAi (and are not the subject of the present application).

Significantly, the Office fails to provide a sufficient reason why those of skill in the art would have combined a reference discussing substrates for RNase H with references describing substrates utilized in siRNA-based methods. Instead, the Office glosses over this difference remarking that "the general use of substituents as claimed was established in the art at the time of the invention."[15] The Office trivializes the important differences in the biological mechanisms of RNAi and RNase H and the particular structural requirements of the substrates dictated by those mechanisms, and ignores the fact that the claimed compounds are unsuitable for decreasing a target nucleic acid through traditional RNase H-mediated mechanisms. As noted above, RNase H-dependent antisense compounds are single stranded and comprise at least four contiguous DNA or DNA-like nucleosides. There would have

[15] Office Action dated April 14, 2009 at page 4.

been no reason for those skilled in the art to have combined teachings from a reference describing substrates utilized in this mechanism with a reference describing RNAi substrates.

Moreover, the Office offers no reason why those of ordinary skill in the art would have selected the *particular* chemical modifications recited in the present claims before applicants' invention from among the nearly limitless number of possible modifications described in the art in order to design and produce the claimed compositions, particularly in light of the limited guidance provided in the cited references regarding the specific type, number, and positioning of chemical modifications that would confer advantageous properties to oligomeric compounds bearing the modifications. The cited references, when considered individually or in combination, thus fail to describe or suggest complementary pairs of siRNA oligomeric compounds consisting of first and second oligomeric compounds that are not covalently linked to each other in which at least one of the first and second oligomeric compounds comprises at least one steroid conjugate moiety attached to a terminal monomeric subunit of the oligomeric compound.

Furthermore, the art of siRNA design at the time of the invention was unpredictable. Since those of ordinary skill in the art could not have anticipated which chemical modifications in siRNA duplexes would have resulted in active compounds, the invention represents a selection from among a vast number of unpredictable possible choices and is therefore non-obvious. It appears that the Office's approach to designing siRNA molecules in view of the vast teaching in the art regarding chemical modification of nucleosides would be to simply try all possible combinations of modifications. Not only is such an approach impossible, given the vast number of combinations of modifications, it also fails to support an obviousness rejection because the art does not support a finding that the claims represent a selection from among predictable possibilities.

In this regard, in *KSR*, the Supreme Court noted that when "there are a *finite* number of identified *predictable* solutions a person of ordinary skill has good reason to pursue the known options in his or her technical grasp."[16] *KSR* involved simple technology with only a few variables; a control pedal and an electronic throttle, each of which was separately known in the art. In *Takeda*, though, the inventors selected a lead compound from among several

[16] *KSR* at 1742 (emphasis added).

hundred for modification and further investigation. In finding non-obviousness, the *Takeda* Court contrasted this situation from that in *KSR*, remarking that, "[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation."[17] Similarly, the invention in *Ortho McNeil Pharmaceuticals v. Mylan Laboratories,* an epilepsy drug, did "not present a finite (and small in the context of the art) number of options easily traversed to show obviousness."[18]

In *KSR*, once the claimed control pedal was designed, there was little doubt that it would work for its intended purpose. Thus, as the Court noted, the invention was selected from among "predictable solutions." In *Takeda*, though, the lead compound (as discussed above, selected from several hundred) was modified in two ways with unpredictable results. To arrive at the claimed compound from the identified lead, a methyl group was homologated, and the resulting ethyl group was moved from one position on a ring to another. Although these are routine modifications, the court found nothing in the art to predict that "performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-postion of the ring, would have provided a broad safety margin."[19] Until the compound was made and tested, its properties could not have been predicted. Similarly, the invention in *Sanofi-Synthelabo v. Apotex* was an isolated enantiomer of a known racemate, about which an expert testified that "no known scientific principle allows prediction of the degree to which stereoisomers will exhibit different levels of therapeutic activity and toxicity."[20] Accordingly, the Federal Circuit upheld a finding of non-obviousness, noting that "a person of ordinary skill in this field would not reasonably have predicted that the dextrorotory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicty."[21]

The issue in the present case is thus whether the selected modifications utilized in the claimed compositions would have been predictable (like the simple electronic control throttle in *KSR*) or unpredictable (like the chemical modifications in *Takeda* or the enantiomers in

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[17] *Takeda* at 1359.
[18] 520 F.3d 1358, 1364 (Fed. Cir. 2008).
[19] *Id.*
[20] 550 F.3d 1075, 1087 (Fed. Cir. 2008 .
[21] *Id.*

Sanofi-Synthlabo). The Office offers no *specific* reasons why those skilled in the art would have reasonably expected before applicants' invention that the claimed modifications present in an siRNA duplex would have yielded active siRNA compounds. Instead, the Office offers only the conclusory statement that "[t]he claimed invention appears to amount to the use of a known oligonucleotide delivery method [cholesterol conjugation] and a known oligonucleltide that would be delivered to cells[siRNA]."[22] Significantly, the Office offers nothing specific to support the notion that siRNA duplexes bearing the chemical modifications recited in the claims would have been reasonably expected to reduce target mRNA before applicant's invention, in light of the highly unpredictable state of the art, similar to the situation at issue in *Takeda*.

According to the Office's reasoning, the compound at issue in *Takeda* would have been obvious due to it close structural similarity to a compound known in the art. As made clear by the Federal Circuit, however, far more than an unsupported assertion of obviousness based upon structural similarity is required to properly establish obviousness in unpredictable art areas. The situation in *Takeda* mirrors that of the presently claimed oligomeric compounds, in light of the upredictability in the art of siRNA design and production.

The Office dismisses the complexity of siRNA design by simply remarking that certain modifications can provide desirable properties and apparently concluding that all modifications therefore would have been obvious. Omitted from that conclusion is the complicated, unpredictable reality that improving any one property may reduce or abolish another property. For example, if one were to adopt the reasoning set forth by the Office, oligomeric compounds modified at every position with 2'-O-methyl groups would have been expected to have desirable resistance to nucleases and to have high affinity for target messenger RNA, when utilized in siRNA molecules, since 2'-O-methyl groups are known to enhance the stability of antisense oligonucleotides.[23] The art reports, however, that such compounds are totally inactive in RNAi, making them unsuitable as siRNA molecules.[24] Many variables influence whether siRNA molecules bearing particular modifications will be active. In the setting of such unpredictability, the Office provides no reasonable basis for

[22] Office action dated April 14, 2009, page 4.
[23] See, for example, U.S. patent number 6,033,910.
[24] Elbashir *et al.*, *EMBO Journal*, 2001, 20, 6877-6888.

selecting the particular modifications recited in the present claims. The Office glosses over this complexity, blithely labeling design and production of the claimed compounds "a mater of optimization," while, in reality, balancing competing properties during the design and development of siRNA molecules has proven to be unpredictable and extremely challenging.

When one considers the state of the art on balance, it becomes clear that the modifications described in the cited references are neither universally beneficial nor detrimental. Rather, the art teaches that modifications may provide benefits or detriments depending upon their particular type, number, and placement within an oligomeric compound. As in *Takdea* and *Sanofi*, at the time of filing, there was no known scientific principle to allow prediction of which modifications would be active in siRNA molecules and which would not. Such level of unpredictability in the art is incompatible with a finding of obviousness.

In light of the unpredictability in the art at the time of the invention, and the fact that the Office has failed to provide credible reasons why those skilled in the art would have designed and produced siRNA compounds bearing the claimed chemical modifications before applicants' invention, compositions comprising the compounds would not have been obvious at that time. Applicants accordingly, respectfully, request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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